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Original Article

The effects of sublingual specific immunization with dermatophagoides farinae drops on asthma and serum CD4+ and CD8+ cell count and IgE levels in children

Haiyan Chen[1*], Jingmei Tian[1*], Haimei Xu[2], Yong Yang[1]

[1]Department of Paediatrics, Shengli Oilfield Central Hospital, Dongying, Shandong, China; [2]Supply Health Center of Shengli Petroleum Administration, Dongying, Shandong, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: To explore the effect of sublingual specific immunization with dermatophagoides farinae drops in children with asthma, and by looking at serum CD4+, CD8+ and IgE. Method: One hundred twenty-six cases of children with mild bronchial asthma who were allergic to dermatophagoides farina were selected. They were randomly divided into the control group (N=63) receiving routine treatment, and the experimental group (N=63) receiving sublingual specific immunotherapy with dermatophagoides farinae drops in addition to the routine treatment for 6 months. The effective rate, serum IgE levels, serum T lymphocyte subsets and lung function indexes before and after treatment as well as adverse reactions during treatment were compared. Result: The experimental group showed significantly higher effective rates, increased serum CD4+, decreased CD8+ and IgE expression than those in the control group (P<0.05). The lung function indexes, airway responsiveness and cough status, daytime and nighttime asthma symptom scores of the experimental group were significantly improved over those of the control group (P<0.05). The duration time of the main symptoms in the experimental group was significantly shorter than that in the control group, and the frequency of recurrent asthma attacks was significantly lower than that in the control group (P<0.05). The two groups showed no significant difference in the incidence of adverse reactions (P>0.05). Conclusion: Sublingual specific immunotherapy with dermatophagoides farinae drops is more effective in treating children with asthma than traditional methods of treatment.

Keywords: Dermatophagoides farinae drops, pediatric asthma, efficacy, CD4+, CD8+, IgE

Introduction

Asthma is a chronic respiratory allergic disease with a complex pathogenesis. It is mainly caused by the imbalance of T lymphocyte subsets or IgE-mediated type I allergic diseases [1, 2]. The treatment methods for children with asthma include bronchial dilator or glucocorticoid inhalation therapy, and theophylline drugs, etc., to relax the bronchus of the child and alleviate the allergic reactions [3]. However, for some children, the effect of conventional treatment is not ideal, and they often experienced frequent asthma attacks [4]. Moreover, according to the survey, new diagnosis of pediatric asthma is increasing yearly [5]. Dust mites are a common cause of asthma in children and widely distributed in nature [6].

The specific immunotherapy formulations allows the patient to be exposed to the allergen at a low dose, so that the immune system can gradually adapt to the allergen [7]. Specific immunity is the only treatment that is considered to be able to target the pathogenesis of allergic diseases. It can not only inhibit progress of the disease, but also have beneficial effects that last longer than the treatment cycle [8, 9]. dermatophagoides farinae drop is a novel desensitization therapy with strong anti-allergic effect and belongs to sublingual specific immunization. Due to its high safety and convenience, dermatophagoides farinae drops work effectively on adult allergic asthma [10]. However, there is little research about the effect of dermatophagoides farinae drops on child with asthma. Studies have shown that when the body frequently encounters allergens, mediator release is mediated by IgE. T lymphocytes are also involved in the development of asthma [11]. In addition, there are also studies showing that asthmatic children have weak

immune systems, which should be strengthened in treatment [12]. However, there are few studies on the role of T cell lymphocyte and IgE during sublingual specific immunization with dermatophagoides farinae drops.

Therefore, we investigated the efficacy of sublingual specific immunization in children with asthma and the effects of serum levels of CD4+, CD8+ and IgE.

Materials and methods

General Information

A prospective analysis was performed on 126 children with mild bronchial asthma allergic to dermatophagoides farinae. They were randomly divided into the control group (63 patients) receiving routine treatment, and experimental group (63 patients) receiving sublingual specific immunotherapy with dermatophagoides farinae drops in addition to routine treatment for 6 months.

Inclusion criteria: children aged 5~9 years who met the diagnostic criteria for childhood asthma; children who were identified as allergic to dust mites by skin prick test. The severity of each child asthma is identified as intermittent, mild persistent or moderate persistent.

Exclusion criteria: children with other serious organ diseases or immune diseases; children who did not respond to hormones or immunosuppressants; children who have used other glucocorticoids or other anti-allergic drugs in the past month; children with cardiogenic asthma; children who were allergic to the medication used in the study.

All the families of the children agreed to participate in the experiment and signed the informed consent form. This experiment has been approved by the Shengli Oilfield Central Hospital ethics committee.

Experimental methods

Treatment methods: Both groups were given conventional treatment for asthma, namely budesonide nebulization and oral ketotifen tablets. Once the child developed an acute condition, glucocorticoids were used for remission. The experimental group was treated with dermatophagoides farinae drops in addition to conventional treatment. Sublingual administration was given daily at the 1st, 2nd, and 3rd week. The concentration of the allergen active proteins were 1 μg/ml, 10 μg/ml, and 100 μg/ml, respectively. The doses were taken from day 1 to day 7 of each week and were sequentially increased in the order of 1 drop, 2 drops, 3 drops, 4 drops, 6 drops, 8 drops, and 10 drops. At the 4th week, the medicine was replaced with 333 μg/ml allergen active protein, 3 drops each time, once a day. The treatment lasted for 6 months. The child in the control groups took drops of vehicle with the same methods and volume.

Outcomes measurement: Before and after the treatment, 5 ml of fasting venous blood was obtained from the two groups in the morning, and centrifuged at a rate of 1500 r/min for 5 min. The superstratum serum was extracted after centrifugation.

Primary outcome measures: The efficacy of treatment between the two groups after treatment was evaluated. Very effective refers to no asthma attacks after treatment, or occasional mild attacks but without drug treatment; effective refers to significant relief of symptoms after treatment, and the symptom score decreasing by 30%~89%. Ineffective means that there is no significant relief of symptoms after treatment. Effectiveness of treatment = (markedly effective number + effective number)/total number × 100%.

Serum IgE levels, serum t-lymphocyte subsets (CD4+ and CD8+) of the two groups were compared before and after treatment.

Secondary outcome measures: The lung function indexes of the two groups were measured before and after treatment. The indexes included forced vital capacity (FVC), first-second forced expiratory volume (FEV1), and peak expiratory flow rate (PEF). The initial respiratory resistance (Rrsc) [13] and the Leicester Cough Questionnaire (LCQ) score [14] were used to assess airway responsiveness and cough in both groups before and after treatment. The asthma symptom scores of the two groups were evaluated during the daytime and nighttime, and the symptoms were scored with 0-3 points from light to heavy. The disappearance time of main symptoms and the number of recurrences were compared. The incidence of

Table 1. General information table

	Test group n=63	Control group n=63	X^2/t	P
Sex			0.000	0.980
Male	37 (58.73)	36 (57.14)		
Female	26 (41.27)	27 (42.86)		
Age			0.032	0.857
≥7	27 (42.86)	28 (44.44)		
<7	36 (57.14)	35 (55.56)		
BMI			0.032	0.859
≥21	31 (49.21)	30 (47.62)		
<21	32 (50.79)	33 (52.38)		
Degree of disease			0.035	0.851
Light	41 (65.08)	42 (66.67)		
Moderate	22 (34.92)	21 (33.33)		
Clinical typing			0.187	0.911
Cough phenotype	21 (33.33)	19 (30.16)		
Wheezing phenotype	22 (34.92)	24 (38.10)		
Intermittent seizures	20 (31.75)	20 (31.75)		
Family history of asthma			0.035	0.853
Yes	40 (63.49)	41 (65.08)		
No	23 (36.51)	22 (34.92)		
Course of disease (year)	2.85±1.67	2.90±1.71	0.166	0.868
Liver function index				
Serum total protein g/L	68.52±2.57	69.01±2.49	1.087	0.279
Glutamic pyruvic transaminase μmol/L	26.12±4.26	26.21±4.19	0.120	0.905
Total bilirubin μmol/L	11.66±2.72	11.58±2.61	0.168	0.867

adverse reactions, including dizziness, headache, loss of appetite, pruritus and drowsiness, were compared between the two groups.

Statistical methods

In this experiment, SPSS 20.0 software (Boyi Zhixun (Beijing) Information Technology Co., Ltd.) was used for statistical analysis of the experimental data. The count data was analyzed by chi-square test, and the measurement data was expressed by mean ± standard deviation. For intragroup before-after comparison, pairwise t test was used; for between-group comparison, independent t test was used, and P<0.05 indicated statistical difference.

Results

Comparison of general data

There were no significant differences in gender, age, and asthma level between the two groups (P>0.05), which were comparable (**Table 1**).

Comparison of effective rate

In the experimental group, the number of very effective, effective, and ineffective treatments was 45, 11 and 7 respectively, and the total effective rate was 88.89%. In the control group, the number of patients treated with very effective, effective, and ineffective treatment was 28, 15 and 20, respectively. The total effective rate was 68.25%. The total effective rate of the experimental group was significantly higher than that of the control group. (P<0.05) (**Table 2**).

Comparison of serum IgE levels before and after treatment in two groups of children

There was no significant difference in serum IgE levels between the two groups before treatment (P>0.05). The serum IgE expression level of the experimental group was (73.82±9.73) IU/ml after treatment. This was significantly lower than that of the control group, which was (86.59±10.26) IU/ml (P<0.05) (**Figure 1**).

Table 2. Comparison of therapeutic effects between two groups of children [n, (%)]

	Test group n=63	Control group n=63	X^2	P
Very effective	45 (71.43)	28 (44.44)	9.412	-
Effective	11 (17.46)	15 (23.81)	0.775	0.379
Ineffective	7 (11.11)	20 (31.75)	7.966	-
Total effective rate	56 (88.89)	43 (68.25)	7.966	<0.001 <0.050

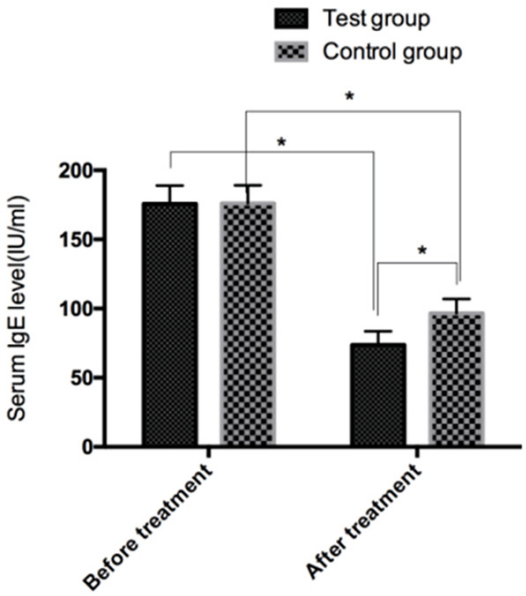

Figure 1. Serum IgE levels before and after treatment in two groups of children. Initially there was no significant difference in serum IgE levels between the two groups (P>0.05). After treatment, the serum IgE expression in the experimental group was significantly better than that in the control group. The difference was statistically significant (P<0.05). Note: *indicated P<0.05.

Comparison of serum CD4+ and CD8+ expression between the two groups before and after treatment

There was no significant difference in serum CD4+ and CD8+ expression between the two groups before treatment (P>0.05). The experimental group showed significantly higher serum CD4+ and lower CD8+ expression than those in the control group (P<0.05) (**Table 3**).

Pulmonary function indicators before and after treatment in two groups of children

There were no significant differences in lung function parameters between the two groups before treatment (P>0.05). The expressions of EEV, FVC and PEF in the experimental group were significantly higher than those of the control group after treatment (P<0.05) (**Table 4**).

Rrsc and LCQ scores before and after treatment in both groups

There was no significant difference in Rrsc and LCQ scores between the two groups before treatment (P>0.05). The Rrsc and LCQ scores of the experimental group were significantly better than those of the control group after treatment (P<0.05) (**Table 5**).

Comparison of daytime and nighttime asthma symptom scores between before and after treatment in both groups

There were no significant differences in the scores of asthma symptoms between the two groups before and after treatment (P>0.05). The daytime and nighttime asthma symptom scores of the experimental group were significantly better than those of the control group after treatment (P<0.05) (**Figures 2** and **3**).

Comparison of the disappearance of major symptoms and the number of recurrent episodes in the two groups

The time of disappearance of the main symptoms of the experimental group was significantly lower than that of the control group (P<0.05). The number of children with asthma recurrence was also significantly less than that of the control group (P<0.05) (**Table 6**).

The incidence of adverse reactions

There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05) (**Table 7**).

Discussion

Asthma is mainly characterized by hyperresponsiveness of the airway and an inflammatory response to airway allergies. Some studies have suggested that there is a correlation between the onset of asthma and the expression of T cells [5]. Some scholars have reported that the level of CD4+ in children with acute attacks of asthma is significantly higher than that of normal children, so it is believed that children with asthma may have immune defi-

Table 3. Comparison of serum T lymphocyte subsets before and after treatment in two groups of children

	Test group (N=63)				Control group (N=63)			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
CD4+ (%)	37.6±2.8	45.2±2.7*	9.43	<0.001	37.7±2.6	38.4±2.3	0.160	0.112
CD8+ (%)	32.1±1.6	25.9±1.4#	7.21	<0.001	31.9±1.5	28.9±1.2	8.12	<0.001

Note: *compared with the control group after treatment, t=15.22, P<0.05, #compared with the control group after treatment, t=23.21, P<0.05.

Table 4. Changes of pulmonary function in two groups before and after treatment

	Test group n=63				Control group n=63			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
FEV (%)	21.31±6.32	40.61±12.33*	9.06	<0.001	21.26±6.82	28.38±9.51	4.83	<0.001
FVC (L)	0.96±0.13	2.21±0.24#	6.35	<0.001	0.98±0.11	1.23±0.21	8.37	<0.001
PEF (L/min)	95.35±18.73	156.39±21.43&	7.02	<0.001	94.84±17.592	118.92±23.61	6.49	<0.001

Note: *compared with the control group after treatment, t=6.234, P<0.05, #compared with the control group after treatment, t=24.39, P<0.05, &compared with the control group after treatment, t=9.327, P<0.05.

Table 5. Rrsc and LCQ scores of two groups before and after treatment

Project	Test group n=63				Control group n=63			
	Before treatment	After treatment	t	P	Before treatment	After treatment	t	P
Rrsc (cmH_2O)	4.59±0.41	2.13±0.32*	7.54	<0.001	4.61±0.42	2.84±0.34	6.01	<0.001
LCQ (Fraction)	9.84±1.05	19.86±1.23#	9.18	<0.001	9.75±1.11	17.21±1.31	4.49	<0.001

Note: *compared with the control group after treatment, t=12.07, P<0.05, #compared with the control group after treatment, t=11.71, P<0.05.

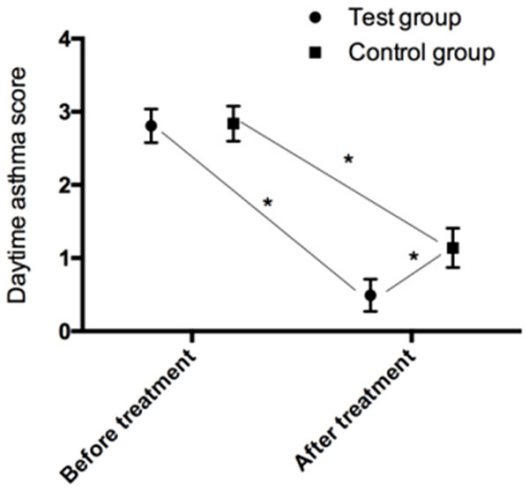

Figure 2. Daytime asthma symptom scores before and after treatment in both groups. There was no significant difference in the scores of daytime asthma symptoms between the two groups (P>0.05). After treatment the scores of daytime asthma symptoms in the experimental group were significantly better than those in the control group, the difference was statistically significant (P<0.05). Note: *indicated P<0.05.

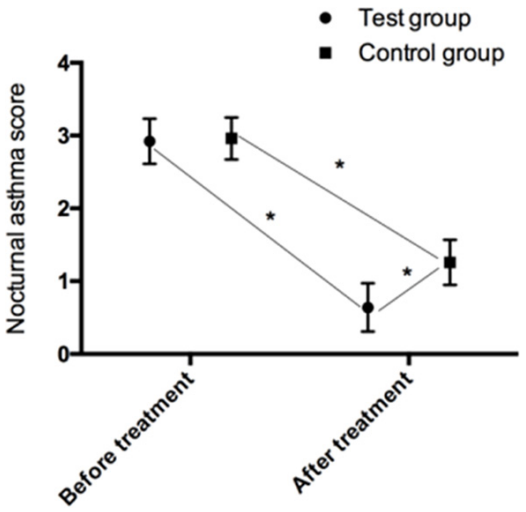

Figure 3. Night asthma symptom scores before and after treatment in both groups. There was no significant difference in the scores of nighttime asthma symptoms before treatment between the two groups (P>0.05). After treatment the scores of night asthma symptoms in the experimental group were significantly better than those in the control group (P<0.05). Note: *indicated P<0.05.

ciency [15, 16]. At present, the drugs commonly used include β2 receptor agonists and bronchodilators such as diastolic bronchus to alleviate allergic reactions. These treatments

Table 6. The disappearance time of major symptoms and the number of recurrent episodes in the two groups

	Test group n=63	Control group n=63	X^2/t	P
The disappearance time of main symptoms (d)	7.15±1.02	8.53±1.12	7.231	<0.001
The number of recurrences was [n, (%)]	9 (14.29)	20 (31.75)	5.420	<0.050

Table 7. The incidence of adverse reactions in two groups of children [n,(%)]

Adverse reaction	Test group n=63	Control group n=63	X^2	P
Dizziness and headache	1 (1.59)	1 (1.59)	-	-
Anorexia	1 (1.59)	0	1.008	0.315
Skin Itch	1 (1.59)	1 (1.59)	-	-
Sleepiness	1 (1.59)	1 (1.59)	-	-
Incidence of adverse reactions	4 (6.35)	3 (4.76)	0.151	0.698

that sublingual immunotherapy with dermatophagoides farinae drops is more effective than routine drug treatment in adult patients with allergic asthma. Studies have shown that Dust mite treatment can significantly improve the lung function of children, which is consistent with our conclusions.

can alleviate symptoms, but with recurrence [17].

Specific immunotherapy is a treatment that has been applied widely in clinical practice [18]. Dermatophagoides farinae drops are a clinically specific immunological drug commonly used in children with asthma. They stimulate the body's immune response through sublingual administration, inhibit the degranulation of lymphocytes, thus reducing the tension of bronchial smooth muscle in children and finally improving symptoms [19-21].

In this study, the results showed that the effective rate of the experimental group was significantly higher than that of the control group after the treatment (P<0.05), indicating that dermatophagoides farinae drops can effectively improve the symptoms of asthma in children, and the effective rate was better compared with the traditional method, which is similar to the results of a previous study [22]. T lymphocytes participate in the cellular immune function of the body and play an important regulatory role in the development of asthma [23]. The results of this study also showed that serum CD4+ was increased and CD8+ was decreased in both groups compared with that before treatment. However, the improvement of serum CD4+, CD8+ and IgE in the experimental group was significantly better than that of the control group (P<0.05) [24, 25]. The above results indicated that the use of dermatophagoides farinae drops could effectively improve the immune function of the children. Zhong C et al also shown

We also compared the Rrsc and LCQ scores and the asthma scores of the daytime and nighttime. The results showed that the Rrsc, LCQ scores and daytime nighttime asthma scores of the two groups were significantly improved compared with those before treatment. The improvement of the experimental group was more obvious than that of the control group (P<0.05). Moreover, the main symptoms of the experimental group disappeared significantly earlier than those of the control group, and the number of recurrences during the treatment was also significantly less than that of the control group (P<0.05). This suggests that dermatophagoides farinae drops can improve the symptoms of asthma in children and their scores in all aspects. Studies [26] indicated that the treatment of allergic asthma by dermatophagoides farinae drops was significantly improved and the number of attacks decreased. The therapeutic effect is getting better and better with the extension of time. Finally, we compared the adverse reactions and found that there was no significant difference in adverse reactions between the two groups (P>0.05), indicating that the treatment of dermatophagoides farinae drops did not increase the incidence of adverse reactions in the treatment and had better safety. Studies [27] investigated the safety of dermatophagoides farinae drops and concluded that the therapeutic drug had higher safety and efficacy.

Sublingual specific immunotherapy with dermatophagoides farinae drops is more effective in treating children with asthma than traditional methods. It can effectively improve the immune

function of children, and does not increase the incidence of adverse reactions. Compared with other immunotherapy, sublingual specific immunotherapy is important for allergy treatment and show better therapeutic effect. However, there are still some deficiencies in this study, for example, there is no comparison between sublingual specific immunotherapy and injection specific immunotherapy, as they may deliver different outcomes [28] and the specific mechanism of action of dermatophagoides farinae drops is not explored. We will continue to make further corrections to these deficiencies in subsequent experiments.

Disclosure of conflict of interest

None.

Address correspondence to: Yong Yang, Department of Paediatrics, Shengli Oilfield Central Hospital, No.31, Jinan Road, Dongying District, Dongying 257000, Shandong, China. Tel: 0546-8770362; E-mail: yongyang5434664@163.com

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